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Absence of pulmonary fibrosis in patients with psoriatic arthritis treated with weekly low-dose methotrexate

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ABSTRACT

Objectives

To analyse pulmonary toxicity in psoriatic arthritis patients treated with weekly low-dose methotrexate.

Methods

A transversal study was carried out to analyse the findings on chest x-rays and high resolution computed tomography, and the results of pulmonary function tests in 27 Caucasian psoriatic arthritis patients treated with weekly low-dose methotrexate. None of them had previous recognized interstitial lung disease.

Results

The median age of the patient cohort was 50 years (range 24-70 years) and the sex ratio was 20M/7F. 17 patients had previously used other disease-modifying antirheumatic drugs. The mean weekly dose of methotrexate was 8.46 mg (range 5-15 mg), the average treatment period was 52 months (range 3-240 months), and the median cumulative dose was 2241 mg (range 300-6520 mg). High resolution computed tomography failed to show alveolar or interstitial involvement in any patient. Diffusing lung capacity for carbon monoxide was mildly altered only in 2 cases. Pulmonary function tests did not show differences between patients with and without recognized risk factors for developing methotrexate-associated lung toxicity identified in rheumatoid arthritis patients (old age, diabetes, hypoalbuminemia, previous use of disease modifying antirheumatic drugs).

Conclusion

In this cohort of 27 psoriatic arthritis patients methotrexate was not associated with pulmonary fibrosis evaluated by means of sensitive imaging findings and pulmonary function tests.

Introduction

Five clinical pulmonary syndromes have been associated with methotrexate treatment (1). Non-cardiogenic pulmonary edema (2, 3) and pleuritis (4, 5) are uncommon and have been reported in patients receiving methotrexate for malignancies at high doses. Pulmonary nodulosis has been described in a rheumatoid arthritis patient (6). Acute interstitial pneumonitis is the most common pulmonary toxicity and is characterized by shortness of breath, non-productive cough, dyspnoea, fever and fatigue with radiographic bilateral interstitial and/or alveolar infiltrates (1). Interstitial fibrosis has been reported in patients receiving methotrexate for rheumatic and non-rheumatic conditions (7-9). Some of them, such as psoriasis, are not associated with the development of interstitial pulmonary fibrosis as a part of the underlying disease process.

In a recent case-control study (10) the strongest risk factors for lung injury identified in patients with rheumatoid arthritis (RA) receiving methotrexate were older age, rheumatoid pleuropulmonary disease, previous use of disease-modifying antirheumatic drugs (DMARDs), low serum albumin, and the presence of diabetes.

Because methotrexate is frequently used in patients suffering from conditions such as RA, dermatomyositis or sarcoidosis, which can be associated with interstitial lung disease, determining the exact role of methotrexate in the development of pulmonary complications in these patients seems to be difficult. Therefore, we conducted a transversal study to analyse the findings found on chest x-rays, high resolution computed tomography (HRCT) and pulmonary function tests (PFT) in a cohort of patients without previous recognized interstitial lung disease who were taking methotrexate as a treatment for psoriatic arthritis, a condition not associated with pleuropulmonary disease.

Patients and methods

Twenty-seven Caucasian patients were recruited. Analysed data included: age, sex, number of years with psoriatic arthritis, presence or absence of axial involvement, previous use of other DMARDs, evidence of previous diabetes or pleuropulmonary disease, consumption of tobacco and alcohol, use of corticosteroids, number of months taking methotrexate, cumulative dose of this drug, presence of recent shortness of breath, fever, cough and/or dyspnoea, laboratory data (leukocyte count, haemoglobin, median corpuscu-

lar volume, platelet count, creatinine, albumin, transaminases), findings on chest x-rays and HRCT. Interstial disease on HRCT was evaluated according to Wells (grade 0: normal, grade I: predominant ground-glass opacity, grade II: mixed pattern, and grade III: predominant reticular pattern and honeycombing). PFT included: forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC, instantaneous forced expiratory flow (FEF50), mean forced expiratory flow during the middle half of the FVC (FEF25-75), residual volume (RV), total lung capacity (TLC), diffusing capacity for carbon monoxide (DLCO) and diffusion per unit of alveolar volume (DLCO/VA). The majority of PFT were expressed as percentages of values obtained from healthy controls matched by age, height and sex. Involvement was expressed as severe (< 50%), moderate (50-65%) or mild (65-80%). Values > 80% were considered normal. Pulmonary methotrexate-associated toxicity was defined according to the criteria of Searles and McKendry (11). All patients were receiving folinic acid (7.5 mg) 24 hours after the weekly dose of methotrexate. A comparison of percentages was carried out using the chi-square test and Fisher's exact test.

Results

The patient cohort consisted of 20 men and 7 women, with a median age of 50 years (range 24-70 years). Seventeen had previously used other DMARDs (7 aurothyomalate, 7 antimalarial drugs, 4 auranofin, 2 sulfasalazine and 1 cyclosporin). Axial involvement was seen in 10 cases. The median number of years with psoriatic arthritis was 11 (range 1-35). Seven patients were current smokers, 3 were diabetic and 2 had previously recognized pulmonary disease (asthma and bronchiectasis). Laboratory data showed: erythrocyte sedimentation rate (ESR) 23 mm/h (range 4-83), C-reactive protein 12 g/l (range 2-66), leukocyte count 6.6 x 10^9/l (range 4.5-10), haemoglobin 118 g/l (range 103-150), median corpuscular volume 74 (range 84-104), platelet count 234 x 10^9/l (range 174-419), albumin 4 g/l (range 2.2-4.6), creatinine 1 g/l (range 0.7-1.2), aspartate transaminase 18 U/l (range 13-22), alanine transaminase 20 U/l (range 14-23), alkaline phosphatase 62 U/l (range 31-98), gammaglutamil transpeptidase 24 U/l (range 14-35). Only two patients had albumin < 2.5 g/l. Chest x-rays showed apical fibrosis in 1 patient and HCRT abnormal findings in 4 patients (3 bronchiectasis and 1 apical fibrosis). Recent dyspnoea and cough were referred only by one patient; his chest x-rays, HCRT and PFT did not show abnormal findings. Methotrexate was administered for a median of 52 months (range 3-240 months), the median current dose of this drug at the moment the study was carried out was 8.46 mg/week (range 5-15 mg/week) and the median cumulative dose was 2,241 mg (range 300-6,520 mg). FEV1% was < 80% of controls in 0 cases, CVF% in 2 cases (74% and 78%), FEV1%/CVF in 0 cases, FEF50% in 4 cases (55%, 61%, 72% and 77%), FEF25-75% in 5 cases (55%, 61%, 61%, 67% and 79%), DLCO in 2 cases (77% and 79%) and DLCO/VA in 2 cases (67% and 71%). PFT were similar in patients with and without axial involvement. Tables I and II show the PFT, comparing data between patients who had previously received other DMARDs and those who did not (Table I) and between patients ≥ 53 years and < 53 years (Table II) respectively.

Discussion

Methotrexate-associated lung toxicity is a potentially life-threatening adverse drug reaction that may be difficult to distinguish from rheumatoid lung or pulmonary infection. Early recognition and drug withdrawal may avoid the serious and sometimes fatal outcome. Because of the high recurrence rate of lung toxicity, a patient who recovers from methotrexate lung injury should not be re-treated with the same drug

Table I. Comparison of PFT between patients who had received previous treatment with other DMARDs and those who did not.

	Total (n = 27)	No previous DMARDs (n = 10)	Previous DMARDs (n = 17)
FEV1 (%)	106 (83-133)	114 (97-133)	101 (83-120)
FVC (%)	98 (74-125)	104 (87-125)	95 (74-107)
FEV1 % VC	111 (101-120)	113 (102-120)	111 (101-120)
MEF 50 (%)	103 (55-160)	112 (69-154)	100 (55-160)
MMEF75/25 (%)	95 (55-132)	102 (61-132)	94 (55-130)
RV (l)	1.2 (0.7-1.9)	1.1 (0.7-1.9)	1.2 (0.7-1.5)
TLC (l)	5.9 (4.1-7)	5.9 (4.5-6.9)	6.1 (4.5-7)
TLCO (%)	106 (77-148)	108 (79-146)	105 (77-148)
TLCO/VA (%)	90 (67-113)	85 (71-113)	92 (67-113)

Table II. Comparison of PFT between patients younger than 53 years and aged 53 years and over.

	Total (n = 27)	≥ 53 years (n = 14)	< 53 years (n = 13)
FEV1 (%)	106 (83-133)	107 (83-123)	105 (85-133)
FVC (%)	98 (74-125)	98 (74-106)	98 (78-125)
FEV1 (%) VC	111 (101-120)	112 (101-120)	111 (106-120)
MEF 50 (%)	103 (55-160)	106 (69-150)	103 (55-160)
MEF75/25 (%)	95 (55-132)	95 (61-128)	97 (55-132)
RV (l)	1.2 (0.7-1.9)	1 (0.7-1.9)	1.4 (0.9-1.6)
TLC (l)	5.9 (4.1-7)	5.7 (4.1-6.7)	6.2 (4.5-7)
TLCO (%)	106 (77-148)	113 (90-148)	100 (77-124)
TLCO/VA (%)	90 (67-113)	94 (71-113)	86 (67-102)

(12). The majority of large series of methotrexate follow-up patients have reported few or no cases of methotrexate-induced lung disease (13-16). Only one multicentric case-control study (29 cases and 82 controls) has been carried out in order to identify the risk factors for this type of toxicity (10). This study included only patients with RA; in this latter condition interstitial fibrosis may be associated with the methotrexate-induced pulmonary toxicity, but also may be a manifestation of the underlying rheumatic disease. In a recent study, McDonagh *et al.* analysed the findings on lung HRCT in 20 RA patients with interstitial lung disease and 20 RA controls without recognized pleuropulmonary disease. HRCT showed pleural or interstitial involvement in 11/20 control patients (17).

The present study was undertaken in a group of patients receiving methotrexate for treatment of a condition like psoriatic arthritis, not associated with pleuropulmonary complications. HRCT and PFT were performed in all patients. HRCT of the lungs has been confirmed to be superior to conventional radiography in the accurate diagnosis of interstitial lung disease, and provides information on disease activity and prognosis, particularly in the differentiation between potentially treatable inflamatory changes and irreversible fibrosis (18). PFT are more sensitive than HRCT in detecting mild abnormalities in patients with pulmonary fibrosis (19).

In this study HRCT failed to show alveolar or interstitial abnormalities in any of the 27 patients and PFT showed only mild declines in some values in a small number of cases. Furthermore, DLCO and DLCO/VA, which specifically measures interstitial involvement, were only mildly altered in 2 cases. Two recent reports have prospectively analysed PFT in patients on methotrexate therapy. Gillespie *et al.* (5) compared pre- and post-treatment PFT in 16 patients who received methotrexate at a high weekly dose (200 mg/week) because of trophoblastic disease (50 mg i.m. on days 1, 3, 5, 7 with folinic acid 7.5 mg orally 24 hours after each methotrexate injection and a 7-day rest period between treatment cycles); they showed a significant reduction in the mean DLCO after treatment without other significant changes. 20% of patients experienced pleuritic chest pain and dyspnoea. Bedi *et al.* (20) have reported a mild and not significant decline in FEF25-75, RV and RV/TLC% values after 6 months of treatment with methotrexate in psoriatic patients.

Pulmonary toxicity can develop at any point during treatment with methotrexate. The majority of patients described suggest that it often occurs early in therapy; 48% (14/29) of patients reported by Kremer *et al.* (12) experienced toxicity by 32 weeks of treatment. In our study only 2 patients had received methotrexate for less than 32 weeks at the time the study was undertaken. No data suggest that the mean weekly dose, single weekly dose versus split doses or the route of administration appear to be important in the predisposition to methotrexate-induced lung toxicity (1).

In the above mentioned multicentric study with RA patients (10) five variables were correlated with methotrexate-associated lung toxicity: older age (odds ratio 5.1), diabetes (odds ratio 35.6), rheumatoid pleuropulmonary involvement (odds ratio 7.1), previous use of DMARDs (odds ratio 5.6) and hypoalbuminemia (odds ratio 19.5). The strongest correlation was between pneumonitis and diabetes. In the present study with psoriatic arthritis patients, only 3 were diabetic; their functional pulmonary status and imaging findings were similar to those in non-diabetic patients. Data obtained from patients who had previously received other DMARDs did not differ from those in patients who had not. Functional tests were similar between patients ≥ 53 years and those <53 years and between patients with and without hypoalbuminemia. Thus, in the present study there were no differences between data obtained from patients with and without recognized risk factors for developing methotrexate-associated lung toxicity; this datum reflects that HRCT and PFT are not valuable to predict patients who will develop this toxic effect in the future.

In summary, PFT and HRCT of the lungs failed to show abnormal findings in a cohort of 27 psoriatic arthritis patients without previous recognized interstitial lung disease receiving weekly low-dose methotrexate during a mean period of more than 2 years. The results were similar when compared between patients with and without recognized risk factors associated with methotrexate-associated pulmonary toxicity.

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